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CASE REPORT

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Takotsubo cardiomyopathy associated with autoimmune polyendocrine syndrome II

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Summary Takotsubo cardiomyopathy (TCM) is a poorly understood condition in which patients with chest pain have a transient ampulla-shaped abnormality of the left ventriculogram, and intact coronary arteries. We report TCM in combination with autoimmune polyendocrine syndrome type II (APS II), which raises new questions about the pathogenesis of TCM.

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Introduction

Takotsubo cardiomyopathy (TCM) is a rare disease that mimics acute myocardial infarction and is named for the characteristic appearance of the left ventriculogram, which resembles a Japanese octopus trap (takotsubo). The etiology and mechanism of this disease are obscure. In this report, a 64-year-old male was diagnosed with TCM and autoimmune polyendocrine syndrome type II (APS II). APS II, also known as Schmidt's Syndrome, is a rare endocrine

disorder in which Addison's disease coexists with autoimmune thyroid disease, or type 1 diabetes mellitus, or both. Coexistence of TCM and APS II in this patient suggests the possibility that hormonal preconditioning may play a role in the pathogenesis of TCM. Recurrent hypotension and hypoglycemia, which are frequently seen in APS II, could be the important triggers of TCM.

Case report

A 64-year-old male with a history of hypothyroidism presented to another hospital with severe fatigue

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and cachexia. He was admitted to the hospital where the diagnosis of hypothyroidism was made. Thyroid hormone supplementation and hyperalimentation were initiated in the hospital. On the sixth hospital day, he developed fever, chest pain, and hypotension with a systolic blood pressure of 80 mmHg. Dopamine infusion was started intravenously to maintain blood pressure. The ECG was remarkable for acute myocardial infarction and bloodwork was remarkable for an elevated creatinine kinase of 1722 IU/l (normal range: 53–288 IU/l) at the eighth hospital day, and subsequently he was transferred to our hospital for further evaluation and treatment.

On admission, his systolic blood pressure was 100 mmHg on a continuous dopamine infusion, and central venous pressure was 2 cmH₂O. The physical examination revealed a short, cachectic body habi-

tus, coarse facial features, sunken eyes, alopecia, vitiligo, and a female hair distribution. An electrocardiogram (Fig. 1) showed sinus rhythm with elongated Q–T intervals and ST-segment elevation in leads I, II, III, aVF, and V2–V6. Terminal T wave inversion was seen in all leads. On transthoracic echocardiogram, he had severely reduced left ventricular contraction at the apical side. Cardiac catheterization demonstrated intact coronary arteries and left ventriculogram showed apical ballooning typical for TCM (Fig. 2).

Laboratory investigations revealed mild elevation of cardiac enzymes; CK-MB peaked at 5.1 U/l. Serum electrolytes revealed sodium 119 mEq/l, potassium 4.0 mEq/l, chloride 96 mEq/l, calcium 6.8 mg/dl, and phosphate 2.8 mg/dl. Endocrine testing was undertaken in response to the electrolyte disorders (Table 1). Free triiodothyronine

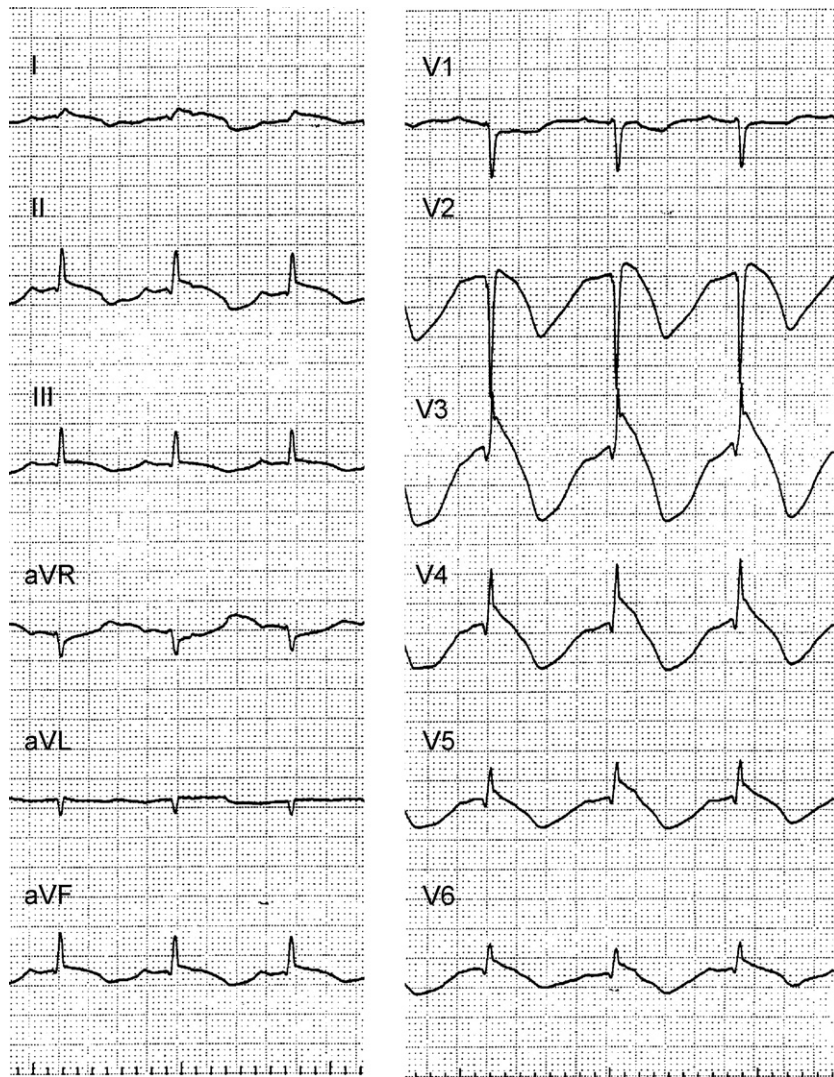


Figure 1 Electrocardiogram on admission.

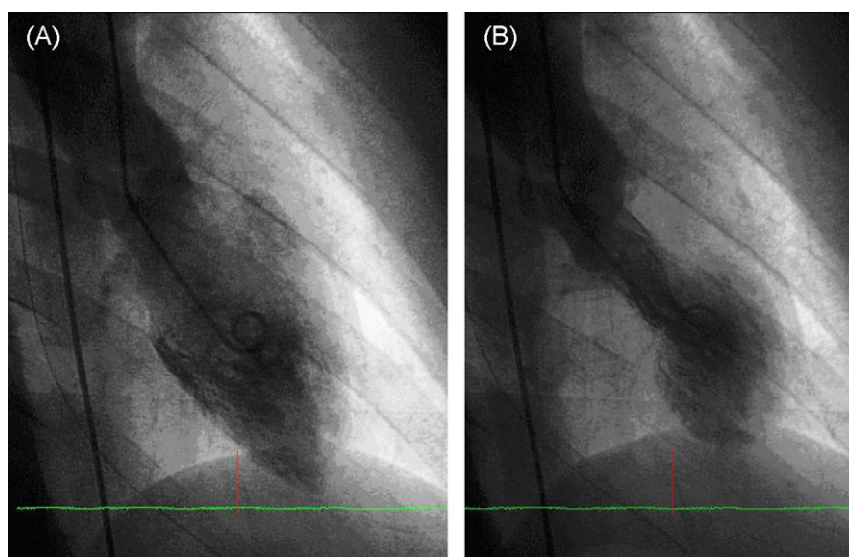


Figure 2 Left ventriculogram from right anterior oblique view at end-diastole (A) and end-systole (B).

(FT3) and free thyroxine (FT4) were suppressed, and thyrotropin (TSH) was elevated. Basal levels of serum catecholamines (noradrenaline, adrenaline, and dopamine) were not increased.

Basal levels of serum cortisol, aldosterone, and adrenocorticotrophic hormone (ACTH) were marginally within normal ranges. Cortisol response to ACTH stimulation test was blunted (Table 2). Antibody panels revealed high levels of anti-thyroglobulin antibodies and anti-thyroid peroxidase antibodies confirming a diagnosis of Hashimoto's disease. He sustained two episodes

of hypoglycemia, in which his serum glucose was <60 mg/dL, further fulfilling the criteria for the diagnosis of APS II, but was not diagnosed with frank type I diabetes.

He was treated with corticosteroids, thyroid hormone, and β -blockade. Left ventricular wall motion recovered by the sixth hospital day, and he did well thereafter.

Discussion

This case reports the coexistence of TCM and APS II in a single patient. TCM remains an enigmatic disorder. Various precipitating factors have been proposed [1]: emotional stress [2], severe physical stress, surgery, medication withdrawal [3], general anesthesia [4], natural disasters [5], thyrotoxicosis [6], multiple endocrine neoplasia [7], and hypoglycemic attacks [8,9]. Tsuchihashi et al. [1] suggested that emotional and physical stress play an important role in TCM. Linking these etiologies, Arora et al. [10] suggested that the TCM results from catecholamine cardiotoxicity, a hypothesis supported by other authors [2,11].

TCM has been reported with hypoglycemic coma in elderly women and with anorexia nervosa, both situations in which catecholamines are elevated [9]. Episodes of excessive catecholamine release under such stressful conditions could trigger TCM after hypoglycemia. This patient was both volume-depleted (low central venous pressure) and hypoglycemic due to APS II. When he was admitted, serum catecholamines were not increased despite the above situation. Because there was no disor-

Table 1 Results of endocrine and thyroid antibody examinations

		Normal range
GH (ng/mL)	0.05	0.03–0.33
LH (mIU/mL)	0.9	0.8–5.7
FSH (mIU/mL)	1.5	2.0–8.3
PRL (ng/mL)	2.6	3.6–12.8
PTH (pg/mL)	4.8	10.0–65.0
FT4 (ng/dL)	0.41	1.00–1.80
FT3 (pg/mL)	1.41	2.20–4.40
TSH (μ U/mL)	8.25	0.27–4.20
TBG (μ g/mL)	29.2	12.0–28.0
Tg Ab (U/mL)	11.5	0.0–32.7
TPO Ab (U/mL)	>60	0.00–0.30
Adrenaline	<0.01	0.00–0.10
Noradrenaline	0.16	0.10–0.50
Dopamine	<0.01	0.00–0.03

GH, growth hormone; LH, luteinizing hormone; FSH, follicle stimulating hormone; PRL, prolactin; PTH, parathyroid hormone; FT4, free thyroxine; FT3, free triiodothyronine; TSH, thyrotropin; TBG, thyroid binding globulin; Tg Ab, thyroglobulin antibody; TPO Ab, thyroid peroxidase antibody.

Table 2 Results of ACTH stimulating test

	Before test	30 min after test	Normal range
Aldosterone (ng/dl)	<1	10.7	3.6–24.0
Cortisol (μ g/dl)	1.0	3.3	4.5–21.1
ACTH (pg/ml)	18.1	11.1	7.4–55.7

ACTH, adrenocorticotrophic hormone.

der of the adrenal medulla in this patient, the lack of an increase in catecholamine excretion was unreasonable. Persisting transient intrinsic catecholamine overshoot in response to hypotension or hypoglycemia before TCM may be possible. External dopamine infusion to maintain blood pressure was another possibility as a triggering factor of TCM.

Hormonal dysfunction may play a role in increasing the susceptibility of patients to TCM under stressful conditions. TCM has higher prevalence among postmenopausal women [12,13], and women with anorexia nervosa [9]. Other reports have speculated that hormones such as estrogen [14,15] and vasopressin [16] play a role in susceptibility to TCM.

The association between TCM and APS II is still unknown. Catecholamine levels in APS II have never been described. Catecholamine deficit can be seen in Bradbury–Eggleston syndrome and dopamine β -hydroxylase deficiency, but has not been part of any reported APS. On the other hand, animal data suggest that adrenocortical androgens from the zona reticularis may induce medullary catecholamine synthesis [17], but no relationship to cortisol levels has ever been demonstrated.

This patient had a complicated endocrinopathy with significant thyroid and adrenal deficits, and a physical examination consistent with longstanding hypogonadism. TCM has been reported once in a patient with adrenal insufficiency and hypothyroidism [18], once with secondary adrenal insufficiency due to isolated ACTH deficiency [19], but not in association with isolated hypothyroidism. There has been a single report of reversible histological injury to the myocardium in a patient with APS II [20]. Severe hyponatremia was also postulated as a cause of functional reduced contractility resulting from increased intracellular calcium concentration due to dysfunction of membrane sodium/calcium ion pump [19]. The theory of transient dysfunction of the sodium/calcium pump due to hyponatremia as a cause of reversible left ventricular function of TCM might be attractive; however, this theory could not explain segmental ventricular dysfunction in TCM.

The role of APS II in this case is not clear, but the multiple stimuli to catecholamine synthesis or

external dose of catecholamine may have been important, or perhaps there was some hormonal preconditioning that promoted the occurrence of TCM during hypotensive or hypoglycemic attacks.

Conclusions

A case in which a patient with TCM in the setting of chronic APS II raises important questions about the possible influence of hormonal preconditioning, and the interplay between hormones of the adrenal cortex and the adrenal medulla. More detailed evaluation of hormone levels in TCM may bring new insight into this unusual and poorly understood condition.

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References

- [1] Tsuchihashi K, Ueshima K, Uchida T, Oh-mura N, Kimura K, Owa M, et al. Transient apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction Angina Pectoris–Myocardial Infarction Investigators in Japan. *J Am Coll Cardiol* 2001;38: 11–8.
- [2] Owa M, Aizawa K, Urasawa N, Ichinose H, Yamamoto K, Karasawa K, et al. Emotional stress-induced ‘apical cardiomyopathy’: discrepancy between the metabolic and sympathetic innervation imaging performed during the recovery course. *Jpn Circ J* 2001;65:349–52.
- [3] Rivera JM, Locketz AJ, Fritz KD, Horlocker TT, Lewallen DG, Prasad A, et al. Broken heart syndrome after separation (from OxyContin). *Mayo Clin Proc* 2006;81:825–8.
- [4] Gavish D, Rozenman Y, Hafner R, Bartov E, Ezri T. Takotsubo cardiomyopathy after general anesthesia for eye surgery. *Anesthesiology* 2006;105:621–3.
- [5] Watanabe H, Kodama M, Okura Y, Aizawa Y, Tanabe N, Chinushi M, et al. Impact of earthquakes on takotsubo cardiomyopathy. *JAMA* 2005;294:305–7.

- [6] Rossor AM, Pearce SH, Adams PC. Left ventricular apical ballooning (takotsubo cardiomyopathy) in thyrotoxicosis. *Thyroid* 2007;17:181–2.
- [7] Frustaci A, Loperfido F, Gentiloni N, Caldarulo M, Morgante E, Russo MA. Catecholamine-induced cardiomyopathy in multiple endocrine neoplasia: a histologic, ultrastructural, and biochemical study. *Chest* 1991;99:382–5.
- [8] Saito Y. Hypoglycemic attack: a rare triggering factor for takotsubo cardiomyopathy. *Intern Med* 2005;44:171–2.
- [9] Ohwada R, Hotta M, Kimura H, Takagi S, Matsuda N, Nomura K, et al. Ampulla cardiomyopathy after hypoglycemia in three young female patients with anorexia nervosa. *Intern Med* 2005;44:228–33.
- [10] Arora S, Alfayoumi F, Srinivasan V. Transient left ventricular apical ballooning after cocaine use: is catecholamine cardiotoxicity the pathologic link? *Mayo Clin Proc* 2006;81:829–32.
- [11] Kono T, Morita H, Kuroiwa T, Onaka H, Takatsuka H, Fujiwara A. Left ventricular wall motion abnormalities in patients with subarachnoid hemorrhage: a neurogenic stunned myocardium. *J Am Coll Cardiol* 1994;24:636–40.
- [12] Dec GW. Recognition of apical ballooning syndrome in the United States. *Circulation* 2005;111:388–90.
- [13] Gianni M, Dentali F, Grandi AM, Sumner G, Hiralal R, Lonn E. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. *Eur Heart J* 2006;27:1523–9.
- [14] Ueyama T, Ishikura F, Matsuda A, Asanuma T, Ueda K, Ichinose M, et al. Chronic estrogen supplementation following ovariectomy improves the emotional stress-induced cardiovascular responses by indirect action on the nervous system and by direct action on the heart. *Circ J* 2007;71:565–73.
- [15] Ueyama T, Hano T, Kasamatsu K, Yamamoto K, Tsu-ruo Y, Nishio I. Estrogen attenuates the emotional stress-induced cardiac responses in the animal model of takotsubo (ampulla) cardiomyopathy. *J Cardiovasc Pharmacol* 2003;42(Suppl. 1):S117–9.
- [16] Ono Y, Kawamura T, Ito J, Kanayama S, Miura T, Kikuchi F. Ampulla (takotsubo) cardiomyopathy associated with subarachnoid hemorrhage worsening in the late phase of vasospasm. *Neurol Med Chir* 2004;44:72–4.
- [17] Charalampopoulos I, Dermizaki E, Vardouli L, Tsatsanis C, Stournaras C, Margioris AN, et al. Dehydroepiandrosterone sulfate and allopregnanolone directly stimulate catecholamine production via induction of tyrosine hydroxylase and secretion by affecting actin polymerization. *Endocrinology* 2005;146:3309–18.
- [18] Oki K, Matsuura W, Koide J, Saito Y, Ono Y, Yanagihara K, et al. Ampulla cardiomyopathy associated with adrenal insufficiency and hypothyroidism. *Int J Cardiol* 2006;108:391–2.
- [19] Sakihara S, Kageyama K, Nigawara T, Kidani Y, Suda T. Ampulla (takotsubo) cardiomyopathy caused by secondary adrenal insufficiency in ACTH isolated deficiency. *Endocr J* 2007;54:631–6.
- [20] Seybold JL, Fowler RA, Chalker R, Berry G, Mihm FG. Histology-proven reversible myocardial injury in Schmidt's Syndrome: a first case. *Endocrinologist* 2002;12:281–4.

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